

REMARKS

This Amendment and Response is submitted in response to the Office Action mailed 25 February 2004. Withdrawal of the rejection and reconsideration with an eye toward allowance is respectfully requested.

Claim Status

Claims 36-39, 45-47, 49, 50, and 52-56 are pending after entry of the present amendment. Claims 36-39, 45-50, and 52-56 stand rejected. Claims 39 and 45 are amended herein for technical clarity. A complete listing of all claims that are, or were in the application, along with an appropriate status identifier, is provided above in the section entitled "Amendments to the Claims". Markings are provided on claims amended in the present amendment. No new matter is entered.

Claim Objections

Claims 39 and 45 were objected to because the Examiner states that the recitation of "a filter" conflicts with the written description of the invention. While not conceding the propriety of the rejection, Applicant has amended claims 39 to recite that the filter is within the second microchannel. Further, and again without conceding the propriety of the rejection, Applicant has amended claim 45 to recite that the reaction module is formed within the second microchannel.

Claim Rejections – 35 U.S.C. §103

Claims 36-39, 45, 46, 49, 50, 53, and 54-56 were rejected under 35 U.S.C. §103(a) as being unpatentable over Wilding (U.S. Patent Number 5,587,128) in view of Bamdad (U.S. Patent Number 6,306,584). As a preliminary matter, and without admitting the propriety of the rejection, Applicant notes that claims 54 and 56 have been cancelled.

Wilding is directed toward a device for amplifying a preselected polynucleotide in a sample. The devices are provided with a substrate microfabricated to include a polynucleotide amplification reaction chamber (see Abstract). Wilding discloses a solid support member, sample handling well, sample inlet port, and microchannels.

Bamdad discloses self-assembled monolayer-forming species including a nucleic acid strand (see col. 11, lines 6-11). Bamdad discloses a one-electrode system including an electrode and a container defining an enclosure, one surface of which is defined by a surface of the electrode. The electrode includes a surface upon which is a self-assembled monolayer. (see col. 21, lines 56-67).

In contrast, Applicant's independent claim 36 recites "a detection well formed in said support member and a detection electrode positioned in said detection well, said detection electrode being provided with a self-assembled monolayer; and a binding ligand" and "a second microchannel formed in said support member and extending between said sample handling well and said detection well for the flow of said fluid sample there between". Independent claim 55 recites "a detection well formed in said support member and a detection electrode positioned in said detection well, said detection electrode being provided with a self-assembled monolayer; and a binding ligand" and "a second microchannel formed in said support member and extending between said reaction module and said detection well for the flow of said fluid sample there between".

Applicants note that to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference teachings. Further, the reference (or references when combined) must teach or suggest all the claim limitations. (See M.P.E.P. §2142).

Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness, as no sufficient suggestion or motivation to modify the reference teachings has been provided. Wilding at col. 19, lines 5-15 recites that "the presence of amplified polynucleotide disposed in either the substrate or in the appliance can be detected by any number of methods...". The Examiner concludes that it is clear that any known means for detecting polynucleotides can be used in the devices of Wilding et. al. (see office action, pages 3-4). Applicant does not so concede. Wilding at most suggests the use of the detection modalities including those listed on col. 19, lines 5-15 *in the device disclosed by Wilding*. Wilding discloses a detection chamber and that a binding moiety capable of binding to an amplified polynucleotide to form a detectable complex may be provided in the detection chamber (see col. 19, lines 41-45). Wilding discloses that the detection chamber may have a bead or other particle capable of binding to the polynucleotide product. At no point does Wilding disclose, suggest, or motivate the use of a detection electrode in the detection chamber. Wilding clearly does not motivate the use of any known means for detecting polynucleotides in the device, as suggested by the Examiner.

The Examiner further suggests that Bamdad teaches that the disclosed electrode structure can be incorporated into microfluidic devices. Applicant respectfully disagrees. Bamdad states at col. 17, lines 41-44 that "it is to be understood that the procedure given in the examples for the preparation of a DNA chip may be applied to the preparation of any nucleic acid chip, such as an RNA chip". This disclosure at most suggests the use of procedures described in Bamdad's examples for the formation of RNA chips. At no point, in the examples or otherwise, does Bamdad disclose or motivate the use of microfluidic components, or formation of chambers or wells in a substrate.

The Examiner's attention is respectfully drawn to *In re Grabiak*, 769 F.2d 729 (1985). The Grabiak Examiner had rejected Grabiak's claimed compound over that of Howe. The Howe compound differed from Grabiak's only by the presence in Grabiak of a sulfur atom instead of a particular oxygen atom. The Grabiak Examiner then cited a textbook reference as showing the interchangeability of oxygen and sulfur. The Court concluded that the Patent Office had not made a *prima facie* case, stating that the textbook reference "does not suggest the interchangeability of sulfur for oxygen *in the ester moiety of the Howe molecule*" *Id* at 732 (emphasis added). The Court stated that the PTO had cited no pertinent reference shown or suggesting to one of ordinary skill in the art the change of a thioester for an ester group. The Court also repeated the statement of *In re Bergel*, 292 F.2d 955, 956-957, "the mere fact that it is *possible* to find two isolated disclosures which might be combined in such a way to produce a new compound does not necessarily render such production obvious unless the art also contains something to suggest the desirability of the combination".

In the present case, Applicant submits that the Examiner has not made a *prima facie* case. No pertinent reference has been provided showing or suggesting to one of ordinary skill in the art the interchangeability of the detection chamber of Wilding with the detection electrode of Bamdad. In *Grabiak*, the Examiner provided a similar prior art structure and a second reference believed to support the motivation to modify one atom for another. The Court still found this insufficient. In the present application, the Examiner relies on Wilding to teach several of Applicant's claimed elements and Bamdad to teach other of Applicant's claimed elements. No teaching or reference has been cited to support the motivation to modify one structure with anything else – let alone the structure in the second reference. The Wilding teaching of various detection methodologies does not suggest the interchangeability with a system described by Bamdad. Bamdad fails to suggest useability or functionality within a microfluidic device. Accordingly, Applicant submits that no pertinent references have been cited to suggest the desirability of placing the SAM-coated electrode of Bamdad into the system of Wilding.

Accordingly, Applicant respectfully submits that the 35 U.S.C. §103(a) rejection of claims 36-39, 45, 46, 49, 50, 53, and 54-56 over Wilding in view of Bamdad is improper and should be withdrawn.

With further regard to claims 54 and 56, Applicant respectfully submits that the cited references, taken alone or in combination, fail to disclose or suggest all limitations of the claims including "an electron transfer moiety".

Wilding is directed toward amplification and a microfabricated substrate. With regard to detection mechanisms, Wilding is limited to disclosure of optical detection and fluorescent labels (see col. 19, line 55 – col. 20, line 41). Wilding does not disclose or suggest electron transfer moieties.

Applicant respectfully submits that Bamdad is silent as to the presence of electron transfer moieties. The Examiner concedes that Bamdad does not explicitly recite an electron transfer moiety, see office action, page 4. However, the Examiner suggests that an electron transfer moiety is inherently present in Bamdad because Bamdad teaches that electron transfer occurs (see office action, page 4), pointing to Bamdad col. 10, lines 47-49, which states "the present invention provides a technique for molecular recognition at surfaces that involves electron transfer through a biological species immobilized at the surface."

Requirements for a rejection based on inherency are discussed in MPEP §2112 noting, "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic" *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) and "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

Applicant respectfully submits that the teaching of Bamdad involving "electron transfer through a biological species immobilized at the surface" (see col. 10, lines 47-49) does not necessarily disclose an electron transfer moiety as recited in Applicant's claims 36 and 55. In fact, Bamdad's system requires detecting electron transfer from a first electrode to a second electrode (which have been brought into close proximity with one another) through the hybridized molecules (see col. 21, lines 21-34). Bamdad accordingly detects electron transfer occurring from one electrode to another connected by a hybridization pair. Accordingly, Applicant submits that Bamdad is silent as to the further presence of an electron transfer moiety, and the presence of an electron transfer moiety does not necessarily flow from Bamdad's disclosure of electron transfer through a biological species.

In summary, Applicant submits that neither Wilding nor Bamdad, nor the references combined disclose or suggest an "electron transfer moiety" as recited in Applicant's independent 54 and 56. Accordingly, Applicant respectfully submits that the 35 U.S.C. §103(a) rejection over Wilding in view of Bamdad is improper and should be withdrawn.

Claims 36-38, 45, 46, 49, 50, and 52-56 were rejected under 35 U.S.C. §103(a) as being unpatentable over Zanzucchi et al. in view of Bamdad.

Zanzucchi is directed toward a system for processing a plurality of tests or syntheses in parallel comprising a sample channel and a plurality of wells, a station for housing the array and an optical system comprising at least one light source and at least one light detector for measuring the samples in the array (see abstract).

Bamdad is discussed above.

Again, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness, as no sufficient suggestion or motivation to modify the reference teachings has been provided. Zanzucchi discloses a series of wells and states that "a well known means of assaying DNA is the hybridization technique. The third well is used for this purpose. The well will be fitted by hybridization probes..." (see col. 10, lines 36-38). The Examiner's position appears to be that Applicant's detection well and binding ligand recited in claims 36 and 55 read on Zanzucchi's hybridization well (see office action, page 6). The Examiner further concludes that it would have been obvious to incorporate the electrode structure disclosed by Bamdad in the hybridization well of Zanzucchi because Bamdad indicates the structure could be used in microfluidic devices (see office action, page 7). As stated above, Applicant's strongly traverse the notion that Bamdad indicates the electrode structure could be used in microfluidic devices. At most, Bamdad discloses techniques for forming a DNA chip having DNA probes on a surface. There is no disclosure or suggestion in Bamdad for forming wells in a surface or of further fluidic components.

Applicant again refers to *Gabiak*, and submits that the Examiner has not made a *prima facie* case. No pertinent reference has been provided showing or suggesting to one of ordinary skill in the art the interchangeability of the hybridization chamber of Zanzucchi with the detection electrode of Bamdad. Indeed, no pertinent reference or motivation has been suggested for providing an electrode as taught by Bamdad, whose stated purpose is detection, with a hybridization chamber disclosed by Zanzucchi for the purpose of hybridizing probes. Indeed, Zanzucchi is even silent as to whether the probes provided in the hybridization well are bound to the surface of the well. Accordingly, Applicant submits that Zanzucchi discloses a hybridization well but does not disclose or suggest positioning a detection electrode in such a well. Bamdad discloses a detection electrode, but does not suggest useability or functionality within a microfluidic device, with other chambers and channels formed in a same substrate, or even a detection well formed in a substrate. Accordingly, Applicant submits that no pertinent references have been cited to suggest the desirability of placing the SAM-coated electrode of Bamdad into the system of Zanzucchi.

Accordingly, Applicant submits that the 35 U.S.C. §103(a) rejection of claims 36-38, 45, 46, 49, 50, and 52-56 is improper, and should be withdrawn.

With further regard to claims 54 and 56, Applicant submits that the references, taken alone or in combination, fail to disclose or suggest an "electron transfer moiety" as disclosed in claims 54 and 56.

That Bamdad does not disclose an electron transfer moiety is discussed above.

Applicant further submits that Zanzucchi fails to disclose or suggest this feature, being limited to disclosure of optical detection (see col. 10, lines 58-60).

Accordingly, Applicant further submits that claims 54 and 56 are patentable over the cited art.

Claim 47 was rejected under 35 U.S.C. §103(a) as being unpatentable over Zanzucchi in view of Bamdad and further in view of Mullis (U.S. Patent Number 4,965,188). As discussed above, Applicant submits that the Examiner has not perfected a *prima facie* case with respect to the combination of Zanzucchi and Bamdad. Applicant further submits that the addition of the Mullis reference does not perfect this *prima facie* case.

Mullis is directed toward a process for amplifying a target nucleic acid sequence including treating strands of the nucleic acid with a molar excess of two oligonucleotide primers and extending the primers with a thermostable enzyme to form complementary primer extension products (see abstract). Mullis does not provide a further motivation for the interchangeability of the detection electrode of Bamdad in the hybridization chamber of Zanzucchi. Accordingly, Applicant submits that the 35 U.S.C. §103(a) rejection of claim 47 is improper and should be withdrawn.

Claims 36, 37, 49, 50, 53, 55, and 56 were rejected under 35 U.S.C. §103(a) as being unpatentable over Segal et. al. in view of Wilding et. al.

Applicant maintains that Segal is disqualified as a prior art reference to the present application (see Applicant's response filed 24 November 2003 and April 28, 2003). The Examiner concedes that Applicant has demonstrated conception of the combination of CMS technology with microfluidic technology, see office action page 11. Applicant respectfully submits that the presently pending claims are drawn to this combination, as evidenced by the declaration of Jon F. Kayyem, accompanying exhibits filed April 28, 2003 and arguments made in the 24 November 2003 and 29 April 2003 responses. However, the Examiner states that Exhibit 1 does not support conception of the structure recited in the claim (see office action, page 11).

Applicants further submit that the Exhibit 1 further shows conception of the combination of sample handling and CMS technology in the context of microfluidics. As shown clearly in Exhibit 1 (first page, first arrow), microfluidics is identified as including "a) separation" and "b) sample prep". Applicant contends that these disclosures support the combination of "a sample handling module" and a "detection well" (claim 36), and the combination of "a reaction module" and a "detection well", and that the only structures not explicitly disclosed in Exhibit 1 are the inlet port and microchannels between these structures. However, these structures would have to be included in the use of the term "microfluidics" to conceptualize a functional system. Thus Applicant submits that Exhibit 1 and the understanding of those of skill in the art as to the meaning of "microfluidics" clearly support conception of the structures recited in the claims.

Accordingly, Applicants submit that microfluidic structures were known, and structures for "CMS technology" were known prior to March 2, 1999. Being provided with the combination of CMS technology with microfluidic technology, as seen in Exhibit 1, the structure recited in Applicant's claim 36 follows,

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both explicitly in the recitation of the combination of "separation" and/or "sample prep" (e.g. a sample handling well) and detection, and implicitly with an inlet port and microchannels.

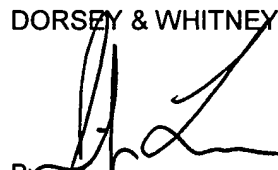
Accordingly, Applicant maintains that claims 36, 37, 49, 50, 53, 55 and 56 are patentable over Segal in view of Wilding, as Segal is unavailable as a prior art reference.

CONCLUSION

Applicants submit the claims are in condition for allowance, and notification of such is respectfully requested. If after review, the Examiner feels there are further unresolved issues, the Examiner is invited to call the undersigned at (415) 781-1989.

Respectfully submitted,

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